Prognosis of Patients with Left Ventricular Diastolic Pressure Abnormality: A Long-Term Survival Study in Patients without Coronary Artery Disease

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Summary

Background: Given that an elevated left ventricular (LV) end-diastolic pressure reflects an abnormality of diastolic function, we analyzed the outcome of this finding in patients without coronary artery disease (CAD).

Hypothesis: The degree to which diastolic dysfunction influences mortality has been confounded in most studies by CAD and advanced age.

Methods: We performed a retrospective study of 876 patients with normal coronary arteries on arteriography. Of these, 115 patients had a left ventricular end-diastolic pressure of ≥ 15 mmHg with an ejection fraction (EF) $\geq 50\%$. We compared the mortality in this group (Group A) with the reported outcome in the general population, adjusted for age, gender, and race, as well as the mortality of a group of patients from the same cohort (Group B) with both diastolic and systolic dysfunction ($n = 60$), defined as a LVEF $< 50\%$.

Results: Follow-up was for a mean of 63 months. In Group A, all-cause mortality was 5% (six patients); two deaths were from cardiac causes. The mean annual mortality in this group (1.2%) was similar to the adjusted annual mortality of the general population (1.1%), and it was significantly lower than the annual mortality (6%) in Group B ($p < 0.03$).

Conclusions: Our study results indicate that diastolic dysfunction with a normal EF, in the absence of CAD and systolic dysfunction, has an excellent prognosis over a long period (5–6 years).

Key words: diastolic dysfunction, abnormal diastolic relaxation, diastolic heart failure, prognosis

Introduction

At present, there is considerable controversy over the best method of diagnosing diastolic dysfunction (DD) and the prognosis for patients presenting with a left ventricular (LV) diastolic pressure abnormality.^{1–8} Upon examination of earlier studies, the conflicting results regarding the prognosis for these patients may primarily arise from the differences in age and prevalence of coronary artery disease (CAD) in the cohort under evaluation.⁹ The majority of reported patients with diastolic dysfunction are elderly (age > 75), predominantly female, and commonly suffer from hypertension and diabetes. In most studies of elderly patients, the prevalence of those with documented CAD is generally $> 50\%$, and the actual percentage, due to unidentified CAD, may be considerably higher. The diagnosis of CAD is generally made on the basis of historical or electrocardiographic data. None of the published studies assessing outcomes and using arteriography excluded patients with CAD. Our analysis of these studies suggests that the outcome in these patients under study primarily derives from age and frequently from coexistent underlying CAD. The contribution of each of these variables is unclear. Our purpose was to determine the contribution that abnormal diastolic function has on long-term mortality in patients who do not have CAD.

Methods

Patient Population

We prospectively recorded clinical, hemodynamic, and angiographic data on 876 consecutive patients into the database of the catheterization laboratory of The University Hospital of the New Jersey Medical School from January 1, 1996 to June 30, 1997. From this cohort, we retrospectively evaluated patients who had a diastolic pressure abnormality, normal coronary arteries as determined by standard arteriography, and a normal ejection fraction (EF). To validate our patient population and to provide a point of comparison, we also selected a second group of patients with an abnormal EF associated with DD and normal coronary arteries. Other than depressed EF, this group had the same inclusion and exclusion criteria as the former group. The institutional review board committee approved the study protocol.

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Definitions

Cardiac catheterization was performed in the postprandial state, and all patients were clinically stable. Diastolic pressure abnormality was defined as a left ventricular end-diastolic pressure (LVEDP) ≥ 15 mmHg. Hemodynamic measurements were determined by a computer algorithm and manually overread. The LVEDP was an average of several pressures obtained through a quiet respiratory cycle and was obtained prior to contrast injection. The active phase of diastolic relaxation is most commonly assessed by the time constant (τ) of the exponential ventricular pressure decline. Such measurements require catheter tip micromanometers that were not used in routine clinical studies we reviewed retrospectively. A recent report by Detsky *et al.* demonstrated a strong correlation between τ and the LVEDP under differing volume and pressure circumstances.¹⁰ Normal coronary arteries were defined as no lesion greater than a luminal irregularity. The LV angiogram was examined visually and was considered normal when the LVEF was $\geq 50\%$ in the absence of wall motion abnormalities. Systolic dysfunction was defined as a LVEF $< 50\%$. Coronary and LV angiograms were visually interpreted by at least two physicians who were not active participants in the present study. Diabetes and hypertension were diagnosed by patient history. Obesity was defined as a body mass index ≥ 30 kg/m².

Exclusions

Patients were excluded if they had more than mild valvular disease, congenital heart disease, hypertrophic cardiomyopathy, myocarditis, end-stage renal disease, alcohol or drug abuse, human immunodeficiency virus positivity, history of angioplasty, open heart surgery, or if their data were incomplete.

Outcome Determination

The primary outcome was total mortality. Information about vital status and cause of death was obtained through query of the National Death Index, which covered vital status reports from January 1, 1996, through December 31, 2001. In addition, since the mean age of the DD group was 58, we obtained the overall population annual death rate for the age group 55–59 years from data provided by the Centers for Disease Control National Vital Statistics for 2001.¹¹ The raw mortality rate of 771/100,000 was adjusted for the 63% female and 58% black patients in our DD cohort.

Statistical Analysis

All baseline and outcome discrete variables are expressed as absolute numbers with percentages. Differences in discrete variables were compared using a chi-square or Fisher's exact test. Continuous variables were expressed as mean values and were compared using the Student's unpaired *t*-test. Difference in time-to-death between the two groups was examined using Kaplan-Meier curves and tested using the log-rank test. The significance level was set at $p < 0.05$. All statistical tests

were two-tailed. Statistical analyses were performed using the Epistat software package (Epistat Services, Richardson, Tex., USA).

Results

Patient Characteristics

We analyzed and included 115 patients with DD and a normal LVEF ($\geq 50\%$) (Group A), and 60 patients with DD and an abnormal LVEF ($< 50\%$) (Group B) (Table I). At the time of cardiac catheterization, the mean LVEDP in Group A was 22 mmHg; 44 (38%) patients had an LVEDP of 15–19 mmHg, 60 patients (52%) had an LVEDP of 20–29 mmHg, and the remaining 11 (10%) had an LVEDP ≥ 30 mmHg. Group B patients differed significantly from Group A patients in only EF ($p < 0.001$) and gender ($p < 0.03$).

Patient Symptoms

All patients in both groups were symptomatic. In Group A, the vast majority (96%) presented with chest pain, while 15% had dyspnea as the study indication; $< 0.035\%$ had signs of congestive heart failure. Because some patients had both chest pain and dyspnea, the percentage exceeded 100%. In Group B, the majority were also studied for chest pain (70%). Dyspnea was present in 25% and congestive heart failure was present in 27% of this group. The high percentage of chest pain in both groups may reflect referral bias or frequently occurring symptoms related to isolated diastolic abnormalities.

TABLE I Patient characteristics

Variable	Systolic dysfunction (n = 60)	Diastolic abnormality (n = 115)
Age (years)	56	58
Male gender, n (%)	37 (62) ^a	44 (37)
LVEF %	35 ^b	59
Race, n (%)		
Black	43 (72)	66 (57)
Hispanic	11 (18)	25 (22)
White	5 (8)	21 (18)
Other	1 (2)	3 (3)
BMI (kg/m ²)	32	31
LVSP $\pm$ SD (mmHg)	150 $\pm$ 26	156 $\pm$ 26
LVEDP $\pm$ SD (mmHg)	23 $\pm$ 5	22 $\pm$ 5
Diabetes, n (%)	14 (23)	25 (21)
Obesity, n (%)	45 (75)	95 (83)
HTN, n (%)	48 (80)	82 (71)

^a $p < 0.001$.

^b $p < 0.03$.

Age, LVEF, BMI, LVSP, and LVEDP, are expressed as mean values. Abbreviations: BMI = body mass index, HTN = hypertension, LVEDP = left ventricular end-diastolic pressure, LVEF = left ventricular ejection fraction, LVSP = left ventricular systolic pressure, SD = standard deviation.

FIG. 1 Survival curves for patients with a left ventricular diastolic pressure abnormality associated with a normal or abnormal ejection fraction (EF). —■— = Normal EF, —◇— = abnormal EF.

Patient Outcomes (Fig. 1)

All patients were followed from the time of diagnosis to the common endpoint of 12/31/2001 for a mean period of 63 months. Of the Group A patients, six (5%) died with a resultant mean annual mortality of 1.2%. Two of the deaths were cardiac and four were deaths from other causes. During a similar time period (2001), the National Center for Health Statistics reported an annual mortality rate of 1.1% for the general population between the ages of 55 and 59 years, adjusted for gender and race. In Group B, 16 (27%) patients died, with an annual mortality of 6%, which was significantly increased when compared with the Group A patients ($p < 0.03$). There was a similar mortality when comparing patients having systolic dysfunction associated with clinical heart failure with those with well-compensated heart failure (i.e., those patients with a depressed EF without signs of congestive heart failure).

Discussion

In this study we excluded patients with CAD in order to ascertain the role, if any, that DD, as evidenced by an elevated end-diastolic pressure, has in survival. Our retrospective study results suggest that patients with DD and normal EF, in the absence of CAD, have an excellent prognosis over a relatively long period (5–6 years). The data show that patients with DD and no structural heart disease have an approximate 1.2% annual mortality. This rate is only slightly and insignificantly higher than the mortality rate reported for the general United States population in 2001 of 1.1%, determined after adjusting for age, gender, and racial distribution.¹¹ We also found that a cardiac cause of death was unusual for this group, occurring in only two patients (0.017%). Our results are in agreement with a smaller study of 51 patients undergoing coronary angiography, which included few patients with CAD (4%) and determined diastolic and systolic function at cardiac catheterization.⁷ They also noted an excellent prognosis, with an annual mortality rate of 1.2% and one cardiac death over a near 5-year period.

The baseline characteristics of the patients with DD with normal LVEF included a high prevalence of hypertension, di-

abetes, and obesity, and the majority were identified as black. Hypertension, diabetes, and obesity are three well-known causes of DD and probably represent the largest component of patients with DD outside of ischemic heart disease.^{12–15} Most studies of isolated DD (i.e., without associated structural heart disease) have included patients older than the mean age of 58 years reported in our study. However, in a recent report by Klapholz *et al.*, attention was called to a black cohort making up 30% of their urban registry population.¹⁶ This cohort was very similar to our patient group, with a younger age and a high prevalence of hypertension and obesity. These observations demonstrate that DD is a significant clinical issue in the middle-aged as well as in the elderly.

In a secondary analysis, we also determined the mortality for a group of patients with DD, no significant CAD, and significant systolic dysfunction (mean EF of 35%). Because we excluded patients with CAD and significant valvular disease, the most common etiologies of systolic dysfunction in our cohort likely included hypertension and diabetes. This group with DD and systolic dysfunction had a 27% mortality over the same 5–6-year time period, with a significantly higher annual mortality of 6% than in the patients with an isolated diastolic abnormality. This occurred despite overall similar baseline characteristics, including no significant difference in the occurrence of hypertension or diabetes, with the exception of gender and clinical heart failure at the time of study entry. These results highlight the contribution of depressed LVEF to the mortality of patients with abnormal diastolic filling pressure.

The prognosis of DD has attracted considerable interest, but the results have not been uniform; investigators have recognized considerable confounding from differences in patient variables and methods of diagnosing both DD and heart failure.^{7, 8, 17–23} Vasan *et al.* summarized the clinical studies of patients with DD and normal EF from 1970 to 1995.⁹ In these studies, the reported annual mortality rate varied from 1.3 to 17.5%, as did the prevalence of CAD which was 100% when patients were recruited from the catheterization laboratory or following an infarction, compared with 52 to 67% when recruitment occurred from the echocardiography or nuclear laboratories. The annual mortality rates in more recent large studies of symptomatic diastolic heart failure were reported to range from 7 to 28% and were mostly due to cardiac deaths, with frequent observations of clinical heart failure and sudden death.^{8, 19, 22, 23} Redfield *et al.* found an association between mild DD as defined by Doppler techniques and increased all-cause mortality despite a low prevalence of a heart failure diagnosis; however, they noted that the presence of even mild DD was closely associated (22%) with CAD in their study.²⁴ These findings are at variance with the observations reported in our study, in which the mortality rate of patients with DD and normal EF approximated the adjusted mortality of the general population, and few cardiac deaths occurred. This difference in the observed mortality between our study and the aforementioned studies is likely due to our definitive exclusion of significant CAD, the low incidence of patients presenting with symptomatic heart failure ($< 0.035\%$), and a more accurate diagnosis of DD. Each of our patients underwent a com-

prehensive and invasive evaluation to determine the LV diastolic pressure and EF as well as to detect coronary atherosclerosis. Without cardiac catheterization, the determination of the extent of CAD as well as the severity of diastolic pressure abnormality are hampered, which has been a limitation of many prior studies assessing the prognosis of patients with DD. The impact that a diagnosis of CAD, independent of DD, has on prognosis has been well documented. Thus, the aforementioned differences in study design further emphasize the impact of CAD on mortality in patients with DD.

The Candesartan in Heart Failure Assessment in Reduction of Mortality (CHARM)-Preserved Trial found that candesartan, an angiotensin receptor blocker, reduced hospital admissions for heart failure, but not cardiovascular death, among patients with New York Heart Association functional class II–IV heart failure and LVEF > 40%.²⁵ We did not record data regarding medication use and were therefore not able to assess their impact, if any, on mortality. However, since the patients with DD and normal EF in our study had a mortality rate that did not differ from that of the general population, adjusting this outcome for treatment with medications would have been unlikely to influence our results.

One of the limitations of our study may include the method of estimating DD. More well-designed techniques for assessing diastolic pressure which require specialized equipment such as catheter tip micromanometers are available but are not routinely used in clinical practice; therefore, clinical estimates of diastolic function will continue to be made from LV diastolic pressures and echocardiographic diastolic filling patterns. Other limitations of our study include its retrospective nature as well as inadequate information regarding the duration of symptoms, which may result in a lead-time bias in assessment of survival times. In addition, the elderly population, which commonly exhibits diastolic heart failure, is not well represented in our patient cohort. This is likely related to the inner-city population serviced by our hospital in addition to the exclusion of patients with CAD, symptomatic heart failure, and significant valvular disease.

Conclusions

We conclude from our data and the above-described studies that diastolic dysfunction, as indicated by abnormal LV diastolic pressure, in the absence of coronary epicardial disease and systolic dysfunction, has an excellent 5–6 year prognosis, with a mortality rate similar to that of the general population. We would further suggest that a high prevalence of CAD, particularly when associated with depressed EF, has the greatest influence on the survival of patients with DD and accounts in part for the increased mortality observed in prior studies in patients with DD.

References

1. Gaasch WH, Zile MR: Left ventricular diastolic dysfunction and diastolic heart failure. *Ann Rev Med* 2004;55:373–394
2. Vasan RS, Levy D: Defining diastolic heart failure: A call for standardized diagnostic criteria. *Circulation* 2000;101:2118–2121
3. Paulus WJ: European Study Group Diastolic Heart Failure. *Eur Heart J* 1998;19:990–1003
4. Zile MR, Brutsaert DL: New concepts in diastolic dysfunction and diastolic heart failure—Part I. Diagnosis, prognosis and measurements of diastolic function. *Circulation* 2002;105:1387–1393
5. Burkoff D, Maurer MS, Packer M: Heart failure with a normal ejection fraction: Is it really a disorder of diastolic function? *Circulation* 2003;107:656–658
6. Maurer MS, Spevack D, Burkoff D, Kronzon I: Diastolic dysfunction: Can it be diagnosed by Doppler echocardiography? *J Am Coll Cardiol* 2004;44:1543–1549
7. Brogan WC, Hillis LD, Flores ED, Lange RA: The natural history of isolated left ventricular diastolic dysfunction. *Am J Med* 1992;92:627–630
8. Pernikil R, Vinson JM, Shah AS, Beckham V, Wittenberg C, Rich MW: Course and prognosis in patients > 70 years of age with congestive failure and normal versus abnormal left ventricular fraction. *Am J Cardiol* 1997;79:215–219
9. Vasan RS, Benjamin EJ, Levy D: Prevalence, clinical features and prognosis of diastolic heart failure: An epidemiologic perspective. *J Am Coll Cardiol* 1995;26:1565–1574
10. Detsky ME, Azevedo ER, Parker JD: Left ventricular isovolumic relaxation is a predictor of left ventricular end-diastolic pressure. *Can J Cardiol* 2003;19:378–382
11. National Center for Health Statistics, CDC: National Vital Statistics. Number of Deaths and Death Rates by age, race and sex: United States, 2001
12. Hogg K, Swedberg K, McMurray J: Heart failure with preserved left ventricular systolic function: Epidemiology, clinical characteristics, and prognosis. *J Am Coll Cardiol* 2004;43:317–327
13. Regan TJ, Lyons MM, Ahmed SS, Levinson GE, Oldewurtel HA, Ahmad MR, Haider B: Evidence for cardiomyopathy in familial diabetes mellitus. *J Clin Invest* 1977;60:884–899
14. Carbello BA, Gittens L: Cardiac mechanics and function in obese normotensive persons with normal coronary arteries. *Am J Cardiol* 1987;59:469–473
15. Inouye I, Massie B, Loge D, Topic N, Silverstein D, Simpson P, Tubau J: Abnormal left ventricular filling: An early finding in mild to moderate systemic hypertension. *Am J Cardiol* 1984;53:120–126
16. Klapholz M, Maurer M, Lowe AM, Messineo F, Meisner J, Mitchell J, Kalman J, Phillips RA, Steingart R, Brown EJ, Berkowitz R, Moskowitz R, Soni A, Mancini D, Bijou R, Sehhat K, Varshneya N, Kukin M, Katz SD, Sleeper LA, Le Jemtel LH, and the New York Heart Failure Consortium: Hospitalization for heart failure in the presence of a normal left ventricular ejection fraction. *J Am Coll Cardiol* 2004;43:1432–1438
17. Brutsaert DL: Diagnosing primary diastolic heart failure. *Eur Heart J* 2000;21:94–96
18. Chen HH, Lainchbury JG, Senni M, Bailey KR, Redfield MM: Diastolic heart failure in the community: Clinical profile, natural history, therapy, and impact of proposed diagnostic criteria. *J Card Fail* 2002;8:279–287
19. Vasan RS, Larson MG, Benjamin EJ, Evans JC, Reiss CK, Levy D: Congestive heart failure in subjects with normal versus reduced left ventricular ejection fraction. Prevalence and mortality in a population-based cohort. *J Am Coll Cardiol* 1999;33:1948–1955
20. Smith GL, Masoudi FA, Vaccarino V, Radford MJ, Krumholz HM: Outcomes in heart failure patients with preserved ejection fraction. *J Am Coll Cardiol* 2003;41:1510–1518
21. Cohn JN, Johnson G, and the Veterans Administration Cooperative Study Group: Heart failure with normal ejection fraction. The V-Heft Study. *Circulation* 1990;81(2 suppl):III48–53
22. Gottdeiner JS, McClelland RL, Marshall R, Shemanski L, Furberg CD, Kitzman DW, Cushman M, Polak J, Gardin JM, Gersh BJ, Aurigemma GP, Manolio TA: Outcome of congestive heart failure in elderly persons: Influence of left ventricular function. The Cardiovascular Health Study. *Ann Intern Med* 2002;137:631–640
23. Kupari M, Lindroos M, Iivanainen AM, Heikkilä J, Tilvis R: Congestive heart failure in old age: Prevalence, mechanisms, and a 4-year prognosis in the Helsinki Aging Study. *J Intern Med* 1997;241:387–394
24. Redfield MM, Jacobsen SJ, Burnett JC, Mahoney DW, Bailey KR, Rodeheffer RJ: Burden of systolic and diastolic ventricular dysfunction in the community: Appreciating the scope of heart failure epidemic. *J Am Med Assoc* 2003;289:194–202
25. Yusuf S, Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJV, Michelson EL, Olofsson B, Ostergren J, for the CHARM Investigators and Committees: Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: The CHARM-Preserved Trial. *Lancet* 2003;362:777–781